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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

BRAINTREE LABORATORIES, INC.,

Plaintiff,

v.

NOVEL LABORATORIES,

Defendant.

Civil Action No. 11-cv-1341 (PGS)

OPINION

SHERIDAN, U.S.D.J.

Plaintiff Braintree Laboratories, Inc. (Braintree) brings this action against Defendant Novel Laboratories, Inc. (Novel) pursuant to the Hatch Waxman Act alleging infringement of U.S. Patent No. 6,946,149 ('149 Patent), a purgative that cleanses the colon in preparation for colonoscopies that is marketed as SUPREP® Bowel Prep Kit (SUPREP). The Court has jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338. Braintree asserts that Novel's proposed generic version of SUPREP infringes claims 15, 16, 18, 19, 20, and 23 of the '149 Patent. Only three issues remained at trial – invalidity based on the principals of obviousness, anticipation, and indefiniteness.[1] In February 2013, the Court conducted a six-day bench trial on Novel's

[1] On January 18, 2013, the Court granted summary judgment to Braintree on its infringement claims, and on Novel's counterclaims for unfair competition and false marking. The Court also denied Novel's motion for summary judgment on its invalidity counterclaim. (ECF Nos. 261, 262).

invalidity counterclaim. This Opinion incorporates the Court's findings of fact and conclusions of law after a thorough and comprehensive bench trial.[2]

1. Parties

Braintree is a corporation organized and existing under the laws of the Commonwealth of Massachusetts, with its principal place of business located in Braintree, Massachusetts. It is a manufacturer of purgative products. Dr. Mark Cleveland and Dr. John Fordtran are the inventors of the '149 Patent. They assigned their interest in the '149 Patent to Braintree.

Novel is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business located in Somerset, New Jersey. Novel is a generic drug manufacturer.

2. The '149 Patent

The '149 Patent is entitled Salt Solution for Colon Cleansing. It describes a composition for inducing purgation of the colon of a patient comprising from about 100 milliliters to about 500 milliliters of an aqueous hypertonic solution comprising or consisting essentially of an effective amount of sodium sulfate, an effective amount of magnesium sulfate, and an effective amount of potassium sulfate without producing any clinically significant electrolyte shifts or using phosphate. It is administered in a split dose regimen. ('149 Patent, Claims 15, 16, 18, 19, 20, and 23 (PTX 0001)). [3]

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[2] At the bench trial, Novel raised an issue with regard to Braintree's standing to bring this action against it for infringement of the '149 Patent. The standing issue was heard and decided at trial, and is not discussed herein.

[3] For the full text of claims 15, 16, 18, 19, 20, and 23, see '149 Patent, PTX 001.

3. Witnesses

There were four important witnesses including two expert witnesses who testified at trial.[4] Since these witnesses shall be referred to throughout the Opinion, their backgrounds are briefly set forth below.[5]

Dr. John Fordtran, M.D. (fact witness)

Dr. John Fordtran is an inventor on the '149 Patent along with Dr. Cleveland. Dr. Fordtran is the director of the Gastrointestinal Analytical Laboratory at Baylor University Medical Center in Dallas, Texas, where he does both clinical and research work in the gastrointestinal field, and also teaches interns, residents, and fellows in gastroenterology. Dr. Fordtran has worked in the gastroenterology field for about 50 years. He has served as chief of internal medicine at Baylor University Medical Center, and as president of the Baylor Research Institute.

Dr. Mark Cleveland (fact witness)

Dr. Mark Cleveland is a named inventor on the '149 Patent. He is the Senior Vice-President of Research and Development and Regulatory Affairs at Braintree Laboratories, and

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[4] There were a number of other witnesses including Robert Raleigh and Thomas Kelly. In addition, Novel presented deposition testimony of Dr. Russell Pellam, Ph.D., Braintree's Director of Business Development and Licensing; Harry Keegan, III, Braintree's CEO and President; Harry Keegan, IV, Braintree's Vice President of Marketing and Sales; Maria Zacharakis, Esq., McCarter & English, LLP; and John McGowan, Braintree's Director of Clinical Research.

[5] Thomas Kelly, CFO of Braintree testified to the commercial success of SUPREP. Novel's cross-examination substantially undermines the thrust of his testimony and the commercial success of the product. As such, the Court finds that it is not a secondary consideration that is entitled to fair weight to show independent evidence of non-obviousness. *Demaco Corporation v. F. Von Langsdorff Licensing Limited*, 851 F. 2d 1387, 1391 (Fed. Cir. 1988); *Ortho-McNeil Pharmaceuticals v. Mylan Labs, Inc.*, 520 F. 3d 1358, 1365 (Fed. Cir. 2008).

has been employed there since 1985. As chief scientist, Dr. Cleveland oversees Braintree's clinical studies, the Braintree clinical development group, the Braintree pharmacology group, and the Braintree toxicology group.

Dr. John F. Johanson, M.D. (expert witness for Novel)

John F. Johanson, M.D., is Novel's expert witness. He is a board-certified gastroenterologist. He has been practicing since 1991, and is currently in private practice in Beloit, Wisconsin as part of a large multispecialty group. Dr. Johanson has had some experience developing drugs, predominantly for constipation and irritable bowel syndrome. He has also been a clinical investigator in clinical trials associated with a pre-colonoscopy bowel preparation. As part of his current practice, Dr. Johanson routinely conducts colonoscopies and prescribes pre-colonoscopy bowel preps. In his twenty years as a practicing gastroenterologist, Dr. Johanson has performed nearly 20,000 colonoscopies. In preparation for those procedures, Dr. Johanson has prescribed many colon cleansing products, such as GoLytely, NuLytely, and the lower volume preps HalfLytely and MoviPrep. On occasion, Dr. Johanson has prescribed SUPREP.

The Court found Dr. Johanson to be an expert in the field of gastroenterology.

Dr. David Peura, M.D. (expert witness for Braintree)

Dr. David Peura, M.D., is Braintree's expert witness. He is a gastroenterologist who has been an emeritus professor at the University of Virginia since 2008. Dr. Peura is responsible for teaching residents and gastroenterology fellows. He also treats outpatients several days a week. Dr. Peura has been a gastroenterologist since 1977. Following medical school, he commenced his internship and medical residency at Letterman Army Medical Center in San Francisco, CA, where he stayed on an extra year as chief resident. Thereafter, Dr. Peura went to Walter Reed

Army Medical Center in Washington, DC, as a gastroenterology fellow. After completing his training, Dr. Peura remained at Walter Reed, initially as a staff member, and later as a director of clinical services, chief of gastroenterology, and consultant to the Army Surgeon General in gastroenterology. As consultant to the Army Surgeon General, Dr. Peura was responsible for overseeing the practice of gastroenterology throughout the Army. He was also responsible for training, and research to make sure that facilities and funding were adequate to carry out clinical research and educational activities. Dr. Peura retired from the Army in 1990 as a Colonel. During his career, Dr. Peura has performed more than 20,000 colonoscopies.

Over the course of his career, Dr. Peura has prescribed numerous colon cleansing products to patients. In the 1980s, Dr. Peura started prescribing commercially available preparations, such as GoLytely. Most recently, Dr. Peura has prescribed SUPREP.

Dr. Peura has approximately 150 or 160 publications in the field of gastroenterology. He was the chairman of the Board of Trustees of the American College of Gastroenterology. Most recently, Dr. Peura was elected as a master of the American College of Gastroenterology – an honor that is only conferred on two or three people a year – and was the president of the American Gastroenterology Association. Dr. Peura has been recognized for his achievements including the Julius Friedenwald Medal from the American Gastroenterology Association, which is the highest honor that the Association gives to any of its members.

The Court found Dr. Peura to be an expert in gastroenterology, gastrointestinal procedures, and the use of preparations to prepare patients for gastrointestinal procedures.

4. Issues Presented

As noted above, having already decided Braintree's infringement claims on summary judgment (ECF Nos. 261, 262), the issue before the Court at trial is the validity of the '149

Patent. Novel sets forth three bases for their contention that the asserted claims of the '149 Patent are invalid. First, Novel contends that the Hechter reference anticipates the asserted claims of the '149 Patent. Second, Novel asserts that the prior art, as understood by a person having ordinary skill in the art (PHOSITA), renders the asserted claims obvious. Finally, Novel avers that the asserted claims of the '149 Patent are invalid because the claim term "purgation" is indefinite under 35 U.S.C. § 112(b).

5. Introduction

This case concerns colonoscopy preparation solutions – often referred to as purgatives. A purgation is "an evacuation of a copious amount of stool from the bowels after oral administration of the solution." (ECF No. 130, p. 11). In 1969 when the colonoscopy procedure initiated, the purgatives became more important. At that time, Drs. Wolfe and Shenga[6] developed a retrograde colonoscopy and the endoscopic excision of polyps. A colonoscopy is a method to probe the full length of the colon using a "snakelike" tube (as described in the N.Y. Times).[7] It was a relatively simple procedure, but a revolutionary breakthrough in cancer treatment. Colon cancer was a known risk among middle aged and older Americans, and colonoscopy is a procedure to treat and diagnose cancer, if any.[8] The colonoscopy allows the physician to view the lumen and remove polyps and other intestinal growths in one procedure. As such, cleansing of the colon prior to the procedure is important. Obviously, a cleaner colon

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6 *See* Douglas Martin, *Dr. William Wolff, Colonoscopy Co-Developer, Dies at 94*, N.Y. Times, September 1, 2011.

7 The parties defined colonoscopy as a "visual examination of the interior of the colon with a long, flexible, fiber optic instrument (colonoscope)."

8 In 2000, "the American College of Gastroenterology anointed colonoscopy as the preferred strategy for colon cancer prevention." Elisabeth Rosenthal, *The $2.7 Trillion Medical Bill,* N.Y. Times, June 2, 2013.

improves the view of the lumen, and allows an unobstructed observation of any polyps or growths.

This case centers on the formulation of the preparatory solutions for a colonoscopy, which were first developed during the 1970s and 1980s. These solutions were generally considered "large volume," isotonic preparations.[9] (T. 950, 23). These large volume, isotonic preparations require a patient to drink about a gallon of the purgative solution (4 liters). Since most patients dislike the taste of the purgative solution (salty) and the amount of solution they are required to drink (a gallon), many patients failed to drink the appropriate volume. This lack of compliance causes an insufficient purgation, which in turn results in a clouded, or less clear view of the colon interior, compromising the results of the colonoscopy.

Since the 1980s, many clinicians and practitioners thought that a low volume purgative would be a better alternative to alleviate patient noncompliance. In 2002, Dr. Fordtran and Dr. Cleveland invented the '149 Patent. It is a low volume, hypertonic[10] purgative marketed as SUPREP.

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[9] Generally, isotonic means a solution having an osmotic pressure that is similar to a reference solution. An isotonic solution containing a poorly absorbable solute, when ingested, has an osmotic pressure that is similar to body fluids and, as a result, does not cause movement of fluid into or out of the bowel. Dr. Peura, Braintree's expert witness, indicated that "an isotonic solution mimics blood." (T. 944, 4-5). Since isotonic solutions try to mimic the blood, the "idea is there's not going to be any net movement of water or the other minerals or electrolytes that are contained in it, or minimal movement, to maintain a balance within the body." (T. 944, 11-15). As such, "the water [that] is incorporated in the solution, remains in the intestine . . . and is eventually eliminated as a bowel movement." (T. 944, 16-22). Most large volume preparations are isotonic.

[10] A hypertonic solution is one having a higher osmotic pressure than a reference solution. A hypertonic solution containing a poorly absorbable solute, when ingested, creates an osmotic pressure gradient between the bowel and body fluids large enough to induce the movement of water from the body into the bowel and thereby produce a purgation. Hypertonic solutions are

The '149 Patent product (SUPREP) is a hypertonic solution. To demonstrate the point, Dr. Peura compared SUPREP to seawater. Seawater contains sodium chloride, and since it is concentrated, it will cause water to be drawn from the body into the intestine causing dehydration. SUPREP is also highly concentrated, but since it contains sulfate salts (rather than sodium chloride) which are not readily absorbed into the body, the sulfate salts hold the water in the solution, and the water does not move into the body to create an imbalance. (T. 945, 1-23). Hence, to Dr. Peura, an important factor in deciding this case is the hypertonicity of SUPREP. At odds with Dr. Peura is Novel's expert witness, Dr. Johanson, who claims that the ions present in the three sulfate salts provide the cathartic effect (T. 492, 2 through T. 493, 16), and that a PHOSITA would focus on the function of ions at the time of the invention. Throughout the analysis, the question is whether, as Braintree contends, 1) the purgative solutions administered to humans react differently depending upon the concentration given, the absorption of the solution, and electrolyte imbalances (T. 950, 19 through T. 951, 9);[11] or as Novel contends, 2) the elements used and the ions that were present in the solutions were known at the time of the '149 Patent.

6. The Level of Ordinary Skill in the Art

Braintree and Novel each drafted their own definition for a person having ordinary skill in the art (PHOSITA). Each party's definition of a PHOSITA is set forth below.

It is Dr. Peura's opinion that a PHOSITA is "someone with a medical or related degree with several years of experience, either researching or developing formulations for use in

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very concentrated solutions. As Dr. Peura explained, seawater has a very high concentration of salt (sodium chloride) and is a prototypical hypertonic solution. (T. 944, 2 through T. 945, 3).

[11] As Braintree's expert stated, "it is not really the ions that's as important as how they are delivered, and also in what concentration that they are delivered to determine how they are going to act in the body." (T. 949, 23 through T. 950, 1).

gastrointestinal procedures, or using the preparations to prepare patients for gastrointestinal procedures." (T. 941, 15-21).

According to Dr. Johanson, a PHOSITA's qualifications are broader than Dr. Peura's definition. Dr. Johanson opined that a PHOSITA has a medical degree or related advanced degree in the medical field, and has an understanding of basic mechanisms for producing diarrhea in sufficient quantity to cleanse the colon in advance of surgical or diagnostic procedures, and has an understanding of normal physiology sufficient to evaluate fluid and electrolyte balance in a patient after administration of a colon cleansing composition. (T. 479, 17 through T. 480, 11).

Although either definition is satisfactory, no matter which definition of PHOSITA is chosen, the analysis herein would remain the same. As such, the Court adopts Dr. Johanson's definition of a PHOSITA.

7. Chronology

Subsequent to the development of the colonoscopy, the dreadful tasting preparatory solutions emerged. Unlike the uniqueness of the colonoscopy developed in around 1969, Novel claims that the underpinnings of the preparatory product had existed, to some degree, as far back as 1885. Hence, the prior art on which Novel relies, as well as the facts of the case, are discussed chronologically in the following sections (Pre-Colonoscopy Era, Post-Colonoscopy Era, and the '149 Patent Development).

Pre-Colonoscopy Era

In this section, the prior art published before the development of the colonoscopy is discussed. Novel contends that the purgative effects of sodium sulfate, potassium sulfate, and

magnesium sulfate have been known for more than a century, and therefore were known to a PHOSITA at the time of the invention.

Brunton, A Text-Book of Pharmacology, Therapeutics, and Materia Medica (1885) (DTX 297)

Novel cites to the reference *A Textbook of Pharmacology, Therapeutics and Materia Medica* written by Sir Thomas Lauder Brunton and published in 1885. The Brunton reference characterizes the sulfates of potassium, sodium, and magnesium as the "more commonly employed" "saline purgatives" and defines purgatives as "substances which cause intestinal evacuations" or purgation. (DTX 297-0013-14). The Brunton reference noted the cathartic and diuretic properties of the sulfate salts. It states:

> Saline cathartics as often used in dilute saline solution owe their use in dropsy to a great extent to their diuretic action. When given in concentrated solution under proper conditions, the benefit they produce by purgation is exceedingly great. These conditions are that the alimentary canal should be freed from food and especially from liquids by previous abstinence for some hours, and that the salt should be given along with the smallest possibly quantity of water. Sulfate of magnesia being soluble in less than its own weight of water is most suitable. (DTX 297-0019).

According to Dr. Johanson, the Brunton reference discloses the same sulfate salts/ions that are found in the '149 Patent solutions, namely, sodium, potassium, magnesium, and sulfate. (T. 506, 24 through T. 507, 10). Moreover, Dr. Johanson found that the Brunton reference identifies these ions as producing "exceedingly great" purgation when they are administered in a "concentrated" solution accompanied with the "smallest possible quantity of water." (T. 506, 18-23). Dr. Johanson concluded that the effects of saline purgatives as described in the Brunton reference are still valid today. (T. 508, 5-6). According to Dr. Johanson, a PHOSITA would use the Brunton reference in the development of a colonoscopy preparatory product. (T. 506, 9

through T. 508, 16). To him, the most important feature of the Brunton reference is that it discusses the use of the same ions that are described in the '149 Patent in concentrated solutions for causing purgation. (T. 507, 1-3).

Dr. Peura found Dr. Johanson's opinion to be inaccurate. To Dr. Peura, there is no teaching in the Brunton reference that talks about combining sulfate salts to achieve an aqueous hypertonic solution, as Brunton "merely lists some of the salts." (T. 991, 19-22).

Jones, Letter to the Editor, Vol. 19, Journal of the American Medical Association 439-440 (1892) (DTX 280)

In an 1892 publication, Dr. Jones wrote a letter to the editor of the *Journal of the American Medical Association* that concerned the chemical properties of the water at Cooper's Well, Mississippi. (DTX 280). The letter is informal and anecdotal. The letter discloses the benefits derived from "the medicinal properties of the mineral water of Cooper's Well, Mississippi." (DTX 280). The Jones reference describes that:

> The mineral water of Cooper's Well (situated about the geographical center of the State of Mississippi) is prompt and decided in its therapeutical effects, which may be classified as 1. Purgative . . . . 1. The Purgative effects are due chiefly to magnesium sulphate (Epsom salts, about 24 grains per gallon); Sodium sulphate (Glaubers salt, about 15 grains per gallon); . . . . 2. The Diaphoretic effects are due mainly to the peculiar salts and to the potassium sulfate (about 6 grains to the gallon). (DTX 280-0003-4).

The Jones reference further states that the "combined effects of the saline ingredients, amounting to 106 grains to the gallon (about one-fourth of an ounce per gallon), are manifest in the dark green copious evacuations from the bowels, the frequent and abundant excretions from the kidneys." The letter concludes that patients with the disease of consumption are not

benefitted, but they may find solace from "the elevation, cool climate and pure, bracing air and exercise over the beautiful hills and ravines covered with lofty long leaf pine." (DTX 280-0004).

In addition to purgation, the Jones reference claims that the ions in the waters of Cooper's Well can be used to treat disorders including acute and chronic alcoholism, gout, chronic malarial poisoning, chronic diarrhea, chronic constipation, and nervous exhaustion. (T. 781, 12 through T. 782, 13).

According to Dr. Johanson, the purgative effects of the ions in the waters of Cooper's Well are still valid as of the time of the '149 patented invention, upon which a PHOSITA would rely. (T. 514, 13 through T. 515, 9; T. 782, 14 through T. 783, 2). Hence, to Dr. Johanson, it is the use of the three sulfate salts (sodium, magnesium, and potassium) together that is important to a PHOSITA.

Dr. Peura is more skeptical. He noted that the Jones reference describes Dr. Jones's personal experience with drinking mineral water from Cooper's Well. (T. 989, 13-18). He concluded that in April, 2002, a PHOSITA would not look back to the Jones reference to solve the problems described in the '149 Patent because:

> We have no idea what the concentrations of any of these constituents are, and how much a person had to ingest of these things. And I think just looking at all of the other associated claims that Dr. Jones makes for this would sort of cast doubt on the reliability of the reference. (T. 989, 19 through T. 990, 8).

In Dr. Peura's opinion, "there's nothing [in Jones] to teach people that they could combine the three sulfate salts that are in the '149 patent, and make an aqueous hypertonic solution safe and effective." (T. 990, 9-19).

Mays, Medical Treatment of Diseases of the Gall-Bladder and Ducts (1905) (DTX 283)

In 1905, the transcript of Dr. Mays's presentation on the treatment of gallbladder disease, gallstones, and inflammation of the gallbladder with laxatives in an attempt to induce bile flow was published in the *California State Journal of Medicine*. (DTX 283). Dr. Mays endorses the use of Carlsbad salts for a laxative effect. Carlsbad salts are a mixture of sodium sulfate, potassium sulfate, sodium chloride and sodium bicarbonate. Dr. Mays states:

> Carlsbad salts should be freely used in these conditions, being given for its laxative effect and also for the purpose of diluting the bile. It is a mixture of sodium sulphate, potassium sulphate, sodium chloride and sodium bicarbonate. It is obtained in both the crystalline and the powdered form, the crystalline form being somewhat the more laxative, as it contains a much larger percentage of sodium sulphate than the powder. Carlsbad salts is to be given in a tumblerful of warm water on rising and no food should be taken for at least an hour afterward, to allow time for it to pass into the bowel. (DTX 283-0001).

According to Dr. Johanson, the disclosure of Carlsbad salts in the Mays reference is relevant because it illustrates the combination of the sulfate salts for purposes of inducing purgation. All of the ions disclosed in the '149 Patent, with the exception of magnesium, are found in Carlsbad salts, which is "given for its laxative effect." (T. 509, 25 through T. 510, 11).

Dr. Peura is leery of the relevance of the Mays reference to the '149 Patent. He declared that the Mays reference "lists some laxatives, it doesn't talk about combining them . . . for a colonic purgation in a safe, effective manner. And it also is discussing treatment of gallbladder disease and nothing to do with colon cleansing." (T. 992, 6-14). Dr. Peura further noted:

> There's nothing here that directs people how much to take, what concentrations to use, what – combining salts, all of these things that we talked about were important. It's not actually the amount, but it's actually the concentration of salts and what salts you use. There's nothing here that would direct one of ordinary skill in the art to come up with that. (T. 992, 15 through T. 993, 3).

Bastedo, Materia Medica: Pharmacology: Therapeutics Prescription Writing For Students And Practitioners (1913) (DTX 282)

The textbook *Materia Medica: Pharmacology, Therapeutics And Prescription Writing For Students And Practitioners*, written by Dr. Walter Bastedo in 1913, teaches about saline cathartics. (DTX 282). The Bastedo reference sets forth the preparation of each of the saline cathartics separately. The Bastedo reference states:

> Preparations and Doses.—I. *Of magnesium*—the oxide, a very light powder, dose, 30 grains (2 gm.); the hydroxide, in the form of milk of magnesia, dose, 2 drams (8 c.c.); and the carbonate, dose 45 grains (3 gm.), are very mildly laxative....The hydroxide is the favorite for children. The citrate (liquor magnesii citratis), dose, half to one bottle of 12 ounces (360 c.c.); *the sulphate (Epsom salt), dose, ½ ounce (15 gm.), very soluble in water*; and the effervescing sulphate, dose, 1 ounce (30 gm.), are more vigorous.
> 2. *Of potassium*—the citrate, 30 grains (2 gm.); the effervescing citrate, 60 grains (4 gm.); the bitarirate (cream of tartar), 30 grains (2 gm.); *and the sulphate, 30 grains (2 gm.)*.
>
> 3. *Of sodium*—the phosphate, 30 grains (2 gm.); the effervescing phosphate, 2 drams (8 gm.); *the sulphate (Glauber's salt), 2 drams (8 gm.)*; and the citrate, 30 grains (2 gm.). (DTX 282-0025).

Dr. Johanson noted that the Bastedo reference states that the saline cathartics are "certain salts of sodium, potassium, and magnesium." (T. 511, 2-5). More importantly, Dr. Johansson noted that the Bastedo reference discloses that there are a limited number of ions, and of the anions or the acid ions, there are citrates, phosphates, sulfates, and tartrates, which are the ones that tend to give cathartic properties. (T. 511, 5-10). According to Dr. Johanson, there are a limited number of saline cathartics available to use for those seeking to formulate safe and effective purgative solutions, and the sulfate salts seem to be the ones that are most commonly used. (T. 510, 25 through T. 511, 10; T. 836, 20 through T. 837, 2).

Dr. Peura contended otherwise because the Bastedo reference does not disclose combining salts into an aqueous hypertonic solution in concentrations that would be safe and effective in inducing purgation. (T. 994, 10-21).

Cohen, The Purgative Action of Magnesium Salts, The Lancet (1935) (DTX 275) and Race, The Purgative Action of Magnesium Salts, Vol. 225, The Lancet (1935) (DTX 286)

In 1935 there were two very brief, one paragraph letters published in the *Lancet* concerning the "purgative action of magnesium salts." (Cohen (DTX 275) and Race (DTX 286)). Although neither Braintree's nor Novel's expert discussed these references in depth, Dr. Johanson believed that the Cohen reference discloses the purgative effects of magnesium sulfate, and discloses an aqueous hypertonic solution that does not produce any electrolyte shifts associated with the magnesium content in the blood. (T. 515, 24 through T. 516, 8). Dr. Johanson concluded that Race discloses the cathartic effect of magnesium and sulfate ions, and that the non-absorption of magnesium sulphate is quite sound. (T. 513, 1-12). Conversely, Dr. Peura discounted both references arguing that neither teaches about the combination of the three sulfate salts in an aqueous hypertonic solution that would result in safe and effective purgation. (T. 993, 15 through T. 994, 3). It is difficult to envision how a PHOSITA could learn critical information from a one paragraph letter.

Post Colonoscopy Era

The utilization of the colonoscopy procedure expanded during the 1970s and 1980s. (T. 544, 20-24). Although the use of the colonoscopy procedure increased during this time, the methods used by patients to prepare for the colonoscopy were problematic. Evidently, physicians employed different preparation techniques and solutions. Initially, it was a common practice to require a patient to undertake a three day liquid diet, imbibe castor oil, and use

enemas. (T. 450, 17 through T. 451, 4). Another preparation technique was the rapid infusion of sodium chloride solutions into the stomach; but this was discontinued because it caused congestive heart failure, and other medical conditions in some patients. (T. 451, 5 through T. 452, 3). As Dr. Peura recalled, in the 1970s, before the existence of commercially available bowel preparation products, physicians "would prescribe enemas, fasting patients to clean their colons; there was a time where we would infuse large quantities of salt solutions, liters of salt solutions, usually through a tube that was put in the stomach to wash out the colon." (T. 935, 11-15). Physicians would also add nonabsorbable sugars like mannitol into the large volume salt solutions in an attempt to hold water in the intestine. (T. 935, 16-18). However, this was found to be "dangerous because the bacteria would ferment the sugar, and methane would be produced causing explosions that occurred inside the patient when cautery was applied." (T. 935, 18-22). Similarly, Dr. Fordtran noted "[m]annitol is fermentable and its metabolism by colonic bacteria yields hydrogen, an explosive gas." (DTX 22-0005).

At the outset of the 1980s, Dr. Fordtran and his colleague Dr. Davis developed a bowel preparation called GoLytely, which was developed to minimize some of the past issues that occurred with prior preparation solutions. In May 1980, Dr. Davis and Dr. Fordtran authored an article entitled *Development of a Lavage Solution Associated with Minimal Water and Electrolyte Absorption or Secretion* in a publication called *Gastroenterology*. (DTX 22). This article describes the development of GoLytely, and their goal to design a solution to produce "total gut perfusion that would not be associated with net water or electrolyte absorption or secretion." (DTX 22-0004). That is, the solution for intestinal lavage would not be absorbed from the intestine or induce a loss of salt and water from the body. (DTX 22-0002). Sodium sulfate was the predominate salt used. (DTX 22-0004).

GoLytely was one of the first commercially available colonoscopy preparation products in the early 1980s. It was a large volume (4 liters), isotonic preparation. (T. 935, 23-25). GoLytely replaced sodium chloride with sodium sulfate to address the safety issues with the sodium chloride infusion approach. It also replaced mannitol with some polyethylene glycol (PEG) in order to prevent explosions. (DTX 22-0004-5).

Cockerill (U.S. Patent No. 4,452,779 (DTX222))

On June 5, 1984, Vernon L. Cockerill was granted United States Patent No. 4,452,779 relating to a "composition for increasing the quantity and quality of the milk produced by lactating mammal . . . such as a farrowing sow or gilt." (DTX 222). The Cockerill patent relates to dry feed supplements for farm animals. (DTX 222, col. 4, ll. 7-12). The Cockerill patent discloses providing sulfate salts in dry feed compositions in amounts of 10 pounds per 2,000 pounds of feed administered. (DTX 222, col. 3, ll. 3-40). In addition, the Cockerill patent explains that the "several components provide a source of both potassium and magnesium, in addition to sodium in amounts which maintain a normal electrolyte balance in the body fluids . . . ." (DTX 222, col. 2, ll. 4-8). Dr. Johanson found that the Cockerill patent is "absolutely" relevant since it discloses the three sulfate salts that are present in the '149 Patent in a hypertonic solution without causing electrolytes shifts. (T. 518, 18 through T. 521, 13; T. 571, 4-17). Dr. Peura undermined that conclusion, finding that the Cockerill patent does not relate to colon purgation, but rather relates to pig feed. He stated:

> Cockerill set out to solve a problem of under-nutrition in piglets. There were young pigs that were being born, and their mothers, the lactating sows, were producing poor quality milk because their breasts were becoming infected and swollen, and the milk glands would become swollen. So what Cockerill decided to do was to try to reduce the amount of fluid in the swollen breasts by giving

> laxatives and diuretic substances that would eliminate the fluid, either through the bowel or the kidney. (T. 979, 1-11).

Goodman and Gilman (1985) (DTX 298)

In 1985, a book entitled *Goodman and Gilman's Pharmacological Basis of Therapeutics* (Goodman and Gilman) (DTX 298) discusses the "mechanism of action of certain laxatives and side effects of certain laxatives." (T. 989, 1-3). Dr. Fordtran noted that it is an "authoritative reference." (T. 386, 5-14). Goodman and Gilman describes a limited number of laxative agents including:

> Various magnesium salts; the sulfate, phosphate, and tartrate salts of sodium or potassium; the disaccharide lactulose; glycerin; and sorbitol. They are poorly and slowly absorbed and act by their osmotic properties in the luminal fluid. (DTX 298-0006).

According to Dr. Johanson, Goodman and Gilman discloses the purgative effects of 15 grams of magnesium sulfate with 250 milliliters of water. (T. 526:11-21). Dr. Johanson asserted that 15 grams of magnesium sulfate is within the range claimed in the '149 Patent. (T. 527:2-5). According to Dr. Johanson, these are key components that a PHOSITA would rely upon prior to the development of the '149 Patent.

Although Goodman and Gilman is comprehensive, Dr. Peura concluded that it does not disclose combining sulfate salts in an aqueous hypertonic solution to develop a safe and effective composition as disclosed in the '149 Patent. (T. 989, 1-12).

Fordtran, A Low-Sodium Solution for Gastrointestinal Lavage, Gastroenterology, January 1990

In January 1990, Dr. Fordtran published an article in the journal *Gastroenterology* entitled *A Low Sodium Solution for Gastrointestinal Lavage*. (DTX 23). This article describes the development of NuLytely, which was a modification of GoLytely that retained its essential

feature of negligible salt and water absorption "and yet has a barely perceptible salty taste because its sodium concentration is only 65 mEq/L." The dosage amount was the same as GoLytely. Its purpose was to improve patient compliance by improving the solution's taste. NuLytely "was developed by removing sodium sulfate, increasing the concentration of PEG, and adjusting the concentration of the other salts." (DTX 23-0001).

Hechter (U.S. Patent No. 4,975,286) (DTX 221)

In December 1990, Herbert Hechter was granted U.S. Patent No. 4,975,286 (DTX 221) entitled Aqueous Cathartic Solution (Hechter). Hechter is an isotonic solution that includes about 3.5 grams per liter of sodium sulfate, about 4.82 grams per liter of magnesium sulfate, about 1.9 grams per liter of sodium bicarbonate, about 3.85 grams per liter of sodium chloride, and about 0.746 grams per liter of potassium chloride. The solution has a volume of between 3 and 4 liters, has a minimal buffering effect on human blood, and is substantially inorganic. *Id.*

Dr. Johanson opines that Hechter renders the asserted claims of the '149 Patent invalid due to anticipation and obviousness. (T. 481, 25 through T. 482, 3; T. 500, 15 through T. 501, 11; T. 503, 5-8). Dr. Johanson enumerated seven reasons why Hechter anticipates the asserted claims of the '149 Patent.

First, Dr. Johanson argues that Hechter discloses an aqueous hypertonic solution. (T. 485, 22 through T. 487, 8; T. 497, 18 through T. 498, 4). To substantiate same, Dr. Johanson focuses on Step 1 of the multi-step process for the preparation of the solution in Hechter. Step 1 entails mixing 60 grams of dry powder with 1 liter of warm tap water (hereinafter referred to as Step 1 Single Liter Solution). Then, in Step 2 of the process, three additional liters of tap water are added to the container and the entire solution is mixed again, and then chilled. (DTX 221,

col. 3, ll. 55-62). Dr. Johanson, zeroing in on the Step 1 Single Liter Solution, found that the Step 1 Single Liter Solution is hypertonic. (T. 486, 5-8; T. 497, 18 through T. 498, 4).

Second, Dr. Johanson opined that the Step 1 Single Liter Solution disclosed by Hechter has the same ions – sodium, potassium, magnesium, and sulfate – as those disclosed in the '149 Patent. (T. 483, 22 through T. 484, 1; T. 493, 10-16). Dr. Johanson explained that ions are important because it is the sulfate ions and magnesium ions, "not the salt," that provides the cathartic effect in the Hechter patent. (T. 492, 2 through T. 493, 16). Since salts, including sulfate salts, typically dissolve in water, the following occurs: (a) the magnesium sulfate breaks down to magnesium ions and sulfate ions; (b) sodium sulfate breaks down to sodium ions and sulfate ions; and (c) potassium sulfate breaks down to potassium ions and sulfate ions. (T. 492, 2 through T. 493, 16).[12]

Third, Dr. Johanson concluded that the amounts of sodium, magnesium, potassium, and sulfate ions found in the Step 1 Single Liter Solution fall within the range of ion amounts in Claim 16 of the '149 Patent.[13] (T. 493, 17 through T. 494, 20). Dr. Johanson arrived at his conclusion by performing a series of calculations concerning the amount of sodium, potassium,

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[12] Dr. Johanson noted that Hechter also includes chloride and bicarbonate ions in addition the sodium, potassium, magnesium, and sulfate ions. (T. 483, 1-9; T. 484, 2-5). The '149 Patent states that bicarbonate and chloride ions may be added to the claimed solutions, if necessary. (T. 484, 6-25). As such, Dr. Johanson found that Hechter discloses the same ions as those disclosed in the '149 Patent. (T. 483, 22 through T. 484, 1).

[13] Claim 16 is a dependent claim covering a composition, reciting: A composition according to claim 15, wherein the solution comprises between about 2 grams and about 40 grams ofNa2S04, between about 2 grams and about 20 grams of MgS04, and between about 1 gram and about 10 grams of K2S04.

magnesium, and sulfate ions found in the Step 1 Single Liter Solution and comparing those amounts with the ranges set forth in Claim 16 of the '149 Patent. (T. 494, 2 through T. 497, 17).

Fourth, Dr. Johanson opined that Hechter discloses inducing purgation of the colon. Dr. Johanson concluded that because 1.6 liters results in a colon cleansing, a lesser amount would presumably cause a purgation. (T. 499, 18 through T. 500, 10; T. 822, 4 through T. 823, 5).

Fifth, Dr. Johanson contended that the '149 Patent discloses an aqueous hypertonic solution between about 100 milliliters and about 500 milliliters, and through some simple calculations, a PHOSITA would have known that Hechter disclosed the same. (T. 485, 17-21). Dr. Johanson asserted that while Hechter discloses that 4 liters is the desirable amount that patients should ingest, patients drinking an average dosage amount of between 1.6 liters and 2.8 liters of solution had their colons cleared sufficiently for a colonoscopy. (T. 485, 1-14; T. 498, 16-23). Since 1.6 liters is 40% of 4 liters, Dr. Johanson concluded that patients who took 40% of the 4 liter solution achieved colon cleansing. (T. 498, 16 through T. 499, 11). Based on this, Dr. Johanson asserted that since 40% of the 4 liter solution in Hechter caused colon cleansing, 40% of the Step 1 Single Liter Solution (i.e. 400 milliliters) would also do so because the 4 liter solution and the Step 1 Single Liter Solution had the same ionic components and amount of ionic components. (T. 497, 18 through T. 499, 11). Dr. Johanson further contended that the amount of ions in that 400 milliliter aqueous hypertonic solution is equal to 40% of the ions in the Step 1 Single Liter Solution, and those amounts are within the "effective amount" ranges claimed in Claim 16 of the '149 patent. (T. 499, 12 through T. 500, 14; T. 821, 2-9). As such, Dr. Johanson concluded that Hechter discloses a 400 milliliter aqueous hypertonic solution, which is within the volume limitation range in the asserted claims of the '149 Patent (about 100 milliliters to about 500 milliliters). (T. 498, 16 through T. 499, 11).

Sixth, Dr. Johanson opined that Hechter discloses a solution that does not produce clinically significant electrolyte shifts. (T. 487, 9 through T. 490, 20).

Seventh, Dr. Johanson contended that Hechter, like the '149 Patent, does not include phosphate. (T. 482, 8-15).

In addition to the above, Dr. Johanson also found that the '149 Patent is invalid due to obviousness. Dr. Johanson relied on the same contentions as set forth in his anticipation argument above, plus one additional argument. That is, that the Hechter patent provides a framework for a PHOSITA to develop his own aqueous solution. (T. 504, 1-9). Dr. Johanson contended that a PHOSITA would have found the 400 milliliter aqueous hypertonic solution disclosed in Hechter by performing the same calculations that Dr. Johanson performed; and a PHOSITA would have: (a) administered the 400 milliliter solution to a patient and assessed the results, and adjusted the electrolytes as necessary, or (b) administered the 400 milliliter solution in a split-dose regimen of two 200 milliliter solutions. (T. 504, 10 through T. 505, 2).

To say the least, Dr. Peura disagrees with Dr. Johanson's interpretation of Hechter. In Dr. Peura's opinion, Hechter does not anticipate and/or make obvious the asserted claims of the '149 Patent. (T. 940, 1-6; T. 955, 21 through T. 956, 3; T. 974, 13-15). Dr. Peura found differently for numerous reasons.

First, Dr. Peura opined that the goal of Hechter was to develop an isotonic, PEG-free bowel preparation because there was a concern that PEG caused the lumen to glisten or shine when viewed during the colonoscopy, and this caused a reflection rather than a clear view of the lumen. This would hinder the physician's view and may cause improper excision of biopsy samples. (T. 956, 4 through T. 957, 3). In order to make the purgative solutions more palatable, PEG was substituted in NuLytly. According to the Hechter patent, PEG diminished the quality

of the view of the colon during a colonoscopy. As a result, market participants attempted to overcome both the dissatisfaction with the taste and quantity of purgative solutions, as well as the reflection in the colonoscopy as a result of the use of PEG. To Dr. Peura, the goal of the Hechter patent was to remove some or all of the PEG – not to develop a hypertonic solution. (T. 956, 4 through T. 957, 3).

Second, to Dr. Peura, Hechter does not teach a PHOSITA to make and administer aqueous hypertonic solutions because Hechter never mentions hypertonic solutions. (T. 961, 8-13; T. 978, 10-14). To the contrary, Hechter "stresses in a number of occasions . . . the importance of maintaining the solution as an isotonic solution, so he [Hechter] actually teaches away from a hypertonic solution." (T. 957, 14 through T. 958, 3; T. 961, 8-16; T. 962, 23 through T. 963, 3; T. 978, 10-14). According to Dr. Peura, rather than disclose the use of hypertonic solutions, Hechter supports the use of isotonic solutions. (T. 957, 21 through T. 958, 3; T. 961, 20-24; T. 967, 11-13).

Third, Dr. Peura concluded that Hechter teaches a PHOSITA that Hechter's solution is isotonic, and that the avoidance of clinically significant electrolyte shifts needs to be done in an isotonic solution. (T. 971, 24 through T. 972, 24). Dr. Peura finds that Hechter disclosed the use of isotonic solutions that are as close to the concentration of blood as possible in order to avoid causing clinically significant electrolyte shifts, (T. 971, 5-17) whereas, the '149 Patent solution makes no attempt to mimic the concentration of blood. (T. 971, 13-17). In contrast to the isotonic solution disclosed in the Hechter patent, the compositions of the '149 Patent avoid clinically significant electrolyte shifts by using a "unique combination of three poorly absorbed salts, in a concentration that doesn't produce electrolyte shifts in the setting of an aqueous hypertonic solution." (T. 971, 18-23; T. 967, 11-13). Dr. Peura concluded that Hechter discloses a colon

cleansing produce that does not produce clinically significant electrolyte shifts, but it does so in an isotonic solution, not a hypertonic solution. (T. 971, 5-12; T. 973, 20 through T. 974:1).

Fourth, Dr. Peura concluded that Hechter does not disclose a solution that is about 100 milliliters to about 500 milliliters. (T. 957:14-20). Dr. Peura asserted that Hechter discloses an intended volume of 4 liters. (T. 958, 2-3). According to Dr. Peura, Hechter describes a solution with a four-step preparation process as follows: (1) 60 grams of a dry powder is placed in the 4 liter container; (2) the 60 grams of powder is diluted with one liter of lukewarm water; (3) 3 liters of tap water is added to the initial 1 liter mixing solution; and (4) the 4-liter solution is chilled. (T. 958, 4-15; T. 959, 25 through T. 960, 14). Dr. Peura opined that there is no teaching in Hechter that the Step 1 Single Liter Solution be administered to patients, or that it can be divided into component parts. (T. 961, 25 through T. 962, 13).

Fifth, Dr. Peura concluded that the hypertonicity of the Step 1 Single Liter Solution is suspect because the Step 1 Single Liter Solution was never tested on a patient and never intended to be given to patients. (T. 960, 15-24; T. 969, 12 through T. 970, 1). According to Dr. Peura, solutions that appear hypertonic in a container are not necessarily hypertonic in the body. (T. 961, 2-7). For example, Coca-Cola is a hypertonic solution, but the sugars and other elements that make it hypertonic are readily absorbed, so it does not act as a hypertonic solution in the body. (T. 961, 2-7). Dr. Peura further asserted that since Hechter discloses a 4 liter isotonic solution, the ions are going to behave very differently in a 4 liter isotonic solution than they would in the Step 1 Single Liter Solution. (T. 969, 12 through T. 970, 1).

Sixth, Dr. Peura does not believe that the Step 1 Single Liter Solution would inherently avoid producing clinically significant electrolyte shifts because it was never administered to a patient and never tested. Dr. Peura further asserted that the Step 1 Single Liter Solution is not

the isotonic solution that Hechter devised or intended to give to patients, as "Hechter goes to great lengths to suggest that to avoid electrolyte shifts the solution has to be isotonic, which required the addition of three additional liters to that one liter solution." (T. 972, 25 through T. 973, 19).

Seventh, while Dr. Peura acknowledged that Hechter discloses that some patients had a sufficient purgation after they ingested 1.6 to 2.8 liters of the 4 liter solution, he had two criticisms of Dr. Johanson's analysis on this issue. First, Dr. Peura asserted that the 1.6 liter solution ingested by patients in Hechter is an isotonic solution, as it was a portion of the 4 liter solution. In contrast, the solution in the '149 Patent is hypertonic. Second, the 1.6 liter solution was administered after patients were given the stimulant laxative Bisacodyl, which makes it different from the '149 Patent. (T. 963, 4 through T. 964, 12).

Eighth, Dr. Peura refutes Dr. Johanson's conclusion that Hechter teaches an aqueous hypertonic solution of magnesium, potassium, sodium, and sulfate ions in the same range as the solutions in the '149 Patent. (T. 967, 5-13). Dr. Peura asserted that the amount of ions may be the same, but the function of those ions is determined by the concentration and how the ions are delivered. The concentrations are important for the physiologic action of a solution. (T. 1038, 21 through T. 1040, 1; T. 1046, 2-7). For example, the concentrations of salts are different in the 1.6 liter isotonic solution and the 400 milliliter hypertonic solution; the concentrations in the isotonic solution are balanced to be equivalent to blood, while the hypertonic solutions are more concentrated. (T. 967, 21 through T. 968, 1).

Ninth, Dr. Peura noted that Hechter fails to disclose the use of potassium sulfate as disclosed in the '149 Patent. (T. 969, 1-3). Hechter also discloses the use of chloride and

bicarbonate ions. These ions were added to the Hechter patent to balance the solution to be close to blood. (T. 970, 2-16). Under any circumstances, it is not the same as the '149 patent.

Finally, Dr. Peura concluded that the asserted claims of the '149 patent are not obvious based on Hechter, either alone or in combination with other prior art. (T. 977, 21 through T. 978, 2). In Dr. Peura's opinion, there is "no teaching in the Hechter patent combined with anything else that [he] found in the prior art that would have led one to combine three sulfate salts in an aqueous hypertonic solution, that would be effective in inducing purgation and still be safe without producing clinically significant electrolyte shifts." (T. 977, 21 through T. 978, 9). He asserts that Hechter does not teach a PHOSITA to make and administer hypertonic solutions because it stresses the importance of isotonic solutions. (T. 978, 10-14). Dr. Peura believes that at the time of the filing of Hechter's patent in 1989, people of ordinary skill in the art "felt that to avoid electrolyte shifts the solution had to be made as close to the composition of blood as possible to avoid movement of electrolytes from one compartment to another." (T. 978, 15-21).

Fleet's Phospho-soda

Fleet's Phospho-soda was a colonoscopy preparation that had been commercially available for years prior to the filing of the '149 Patent application in April 2002. (T. 384, 4-6; T. 505, 10-12). Fleet's Phospho-soda was a phosphate-based, low volume hypertonic solution that was used to clean the colon in preparation for a colonoscopy. (T. 981, 19-25). It improved patient compliance due to its low volume dosage. (T. 295, 24 through T. 251, 1). Dr. Fordtran stated:

> With a low volume solution like Fleet's you have a small volume to drink, and once you swallowed that small volume you're going to get the cathartic effect of the full dose. So you don't have to drink the water, the water's there mainly for safety and so people could

> drink the full dose, and would drink the small dose, and so, compliance was better in terms of in guessing [sic] the full amount of the purgative, and results of colon cleansing were better. (T. 458, 20 through T. 459, 2).

Fleet's Phospho-soda was administered in a split dose fashion. (T. 505, 3-9). Split dosing in a colonoscopy preparation is beneficial in producing a clean colon for two reasons: (1) it brings the time of the last purgation of the colon closer in time to the time of the colonoscopy, and (2) it helps to reduce the volume of solution that the patient needs to take. (T. 252, 1-10).

Anecdotal evidence of health issues resulting from Fleet's Phospho-soda were mounting throughout the early 2000s, and FDA warnings were published. (T. 785, 11-13). Before April 2002, it was known that Fleet's Phospho-soda had safety concerns, particularly when administered to the elderly, patients with diabetes or other ailments of the kidneys, due to complication from the use of phosphate. (T. 459, 6-18; T. 548, 9-23; T. 554, 18 through T. 556, 18; T. 785, 11-15; T. 948, 19 through T. 949, 4; T. 1065, 13-16). Fleet's Phospho-soda was voluntarily removed from the market in December 2008 by the manufacturer due to safety concerns. (T. 561, 24 through T. 562, 7; T. 1002, 8-12; T. 1066, 2-5).

Cohen, 37 Dis. Colon Rectum, 689-696 (1994) ("Cohen 1994") (DTX 276)

In 1994, Stephen M. Cohen, M.D. published an article entitled *Prospective, Randomized, Endoscopic-Blinded Trial Comparing Precolonoscopy Bowel Cleansing Methods* in the journal *Diseases of the Colon and Rectum*. (DTX 276). The article describes a study conducted by Dr. Cohen that compared GoLytely, NuLytely, and Fleet's Phospho-soda to determine any changes in either patient compliance or cleansing ability. *Id.*

Dr. Cohen found with respect to Fleet's Phospho-soda that "[i]t seems to be of paramount importance for the patients to receive the second dose of sodium phosphate rather than ingesting

the entire dose the night before the procedure because it appeared to cleanse the colon better." (DTX 276-0007). "The overall assessment of the three lavage solutions clearly favored the smaller volume" Fleet's Phospho-soda, and there were more cases of "unacceptable preparation" with GoLytely and NuLytely. *Id.* At the end of the study, Dr. Cohen recommended the use of Fleet's Phospho-soda as a precolonoscopy bowel preparation, as he concluded that Fleet's Phospho-soda "was not associated with any clinically significant problem, was preferred by patients and was more effective in colon cleansing." *Id.* Dr. Cohen noted that there was transient hyperphosphatemia, which may limit the use of this cleansing agent in patients with acute or chronic renal failure. *Id.*

Aronchick (U.S. Patent No. 5,616,346 (1997)) (DTX 292)

In 1997, Craig Aronchick was granted a patent for a tablet or capsule containing sodium phosphate to cause purgation of the colon. (DTX 292). The patent was intended to improve patient compliance by using a tablet rather than having patients endure the "decidedly unpleasant, bitter, noticeably saline taste" of purgative solutions. (DTX 292, col. 2, ll. 39-41; DTX 292, col. 3, ll. 35-52).

According to Dr. Johanson, the Aronchick patent addresses the issue of decreasing the volume required in colonoscopy preparation solutions to improve patient compliance. (T. 533, 20 through T. 534, 11). Dr. Johanson also notes that the Aronchick patent discloses the split-dosing regimen associated with the administration of Fleet's Phospho-soda. (T. 534, 12-22).

In Dr. Peura's opinion, "Aronchick doesn't discuss a solution, it discusses a solid formulation. And in addition, Aronchick has phosphate, which is clearly excluded as one of the essential claims of the patent." (T. 981, 15-18). Dr. Peura further opined that the hypertonic solutions in the asserted claims of the '149 Patent would not have been obvious to a person of

ordinary skill in the art in April 2002 based on the disclosure of the Aronchick patent, either alone or in combination with other prior art. (T. 981, 8-13).

Schiller, Journal of Clinical Gastroenterology (1999) (DTX 289)

In 1999, Dr. Schiller, a colleague of Dr. Fordtran at Baylor, published an article entitled *Clinical Pharmacology and Use of Laxatives and Lavage Solutions* in the *Journal of Clinical Gastroenterology* (DTX 289). The Schiller article summarizes the information known at the time about the categories of laxatives and lavage solutions. (DTX 289-0002). According to Schiller, laxatives are drugs that induce defecation, and purgatives or cathartics are a subcategory of laxatives. *Id.*

According to Dr. Johanson, a PHOSITA would rely upon the Schiller article mainly for two reasons. (T. 535, 10 through T. 539:2). First, the Schiller reference discloses the laxative effects of magnesium and sulfate. *Id.* Notably, the Schiller reference discloses that magnesium is a poorly absorbed ion that is found in many laxative preparations, and references a study where a single dose of sodium sulfate in an amount within the range set forth in the '149 Patent produced severe diarrhea. (T. 537, 21 through T. 538, 20). Second, the Schiller reference discloses giving these osmotic agents in hypertonic solutions. (T. 538, 6-13). To Dr. Johanson, it is obvious that the Schiller reference makes the '149 Patent obvious. (T. 535, 10 through T. 539, 2).

Dr. Peura reiterated his previous objection to the prior art, opining with respect to Schiller, "there's nothing here to teach that combining the laxatives listed here would be safe and effective, especially in forming a hypertonic solution." (T. 991, 5-7).

Martindale, The Complete Drug Reference (1999) (DTX 003A)

At about the same time as the Schiller reference, the *Complete Drug Reference* by Martindale was published in 1999. (DTX 3A). It is a compendium of a number of drugs, electrolytes, and chemical compounds, and describes their functionality and usage. (T. 522, 12 through T. 523, 1; T. 988, 2-13). Dr. Johanson contended that a PHOSITA would have reviewed the Martindale reference and found the asserted claims of the '149 Patent obvious for several reasons. First, the Martindale reference is a drug compendium, and this is the first source that a drug formulator would review. (T. 522, 12-18). Second, the Martindale reference discloses that magnesium sulfate, potassium sulfate, and sodium sulfate are osmotic laxatives. (T. 523, 6 through T. 525, 11). And third, the Martindale reference details the dosage of magnesium sulfate that produces "rapid bowel evacuation." (T. 523, 6-16). According to Dr. Johanson, taken together, these disclosures teach the use of sulfate salts and dosages prior to the '149 Patent. (T. 522, 12 through T. 525, 11).

Dr. Peura minimized Dr. Johanson's conclusion because the Martindale reference does not disclose the combination of magnesium sulfate, potassium sulfate, and sodium sulfate into an aqueous hypertonic solution that would be safe and effective for inducing purgation of the colon. (T. 988, 2-22). Martindale only provides information about individual salts. (T. 988, 9-13). In Dr. Peura's opinion, "there's nothing [in Martindale] that would teach that you could combine these salts that are listed here, into an aqueous hypertonic solution that would be safe and effective" as described in the '149 patent. (T. 988, 14-22).

Borody '403 (U.S. Patent No. 5,858,403) (1999) (DTX 293) and Borody '268 (U.S. Patent No. 6,103,268 (2000) (DTX 294)

In 1999 and 2000, Thomas J. Borody was issued two patents, one entitled Picosulfate-Containing Preparation for Colonic Evacuation (U.S. Patent No. 5,858,403) (Borody '403) (DTX 293) and a second Administering Osmotic Colonic Evacuant Containing a Picosulfate (U.S. Patent number 6,103,268) (Borody '268) (DTX 294). These patents discuss the same technical field and rely upon similar background art. (DTX 293; DTX 294; T. 530, 18 through T. 531, 5; T. 985, 1-9). Dr. Johanson described the two Borody patents as being "very similar" (T. 530, 18-22), and Dr. Peura noted that there are no substantial differences between the two Borody patents. (T. 985, 1-9).

Borody '403 and Borody '268 disclose the administration of an osmotic colonic evacuant in the form of a tablet or capsule that is comprised of a phosphate based laxative or a sulfate based laxative comprising sodium picosulfate used in conjunction with a diluent. (DTX 293, Abstract; DTX 294, Abstract; T. 774, 16-23 through T. 775, 15; T. 983, 17-25). Along with the objective of providing an osmotic colonic evacuant that does not cause "arrythmia, dehydration, hypotension, marked electrolyte and fluid shifts, marked weight loss, cardiac deaths, nausea/vomiting or fainting when ingested by a patient" (DTX 293, col. 2, ll. 66; DTX 294, col. 3, ll. 5-9), the Borody patents overcame the problems of "bad taste and foaming without sacrificing the excellent bowel-cleaning characteristics of the phosphate-based lavage solution." (DTX 293, col. 2, ll. 57- 60; DTX 294, col. 2, ll. 63-66).

According to Dr. Johanson, the Borody patents reiterate the concerns regarding patient non-compliance with the 4 liter colonoscopy preparation products, and the shift back to smaller volume preparations, like Fleet's Phospho-soda. (T. 528, 3-12; T. 529, 8 through T. 531, 5).

In Dr. Peura's opinion, Borody '403 "discusses a solid formulation, and there's nothing here that would teach one to use a combination of sulfate salts in a . . . aqueous hypertonic solution to induce purgation, and not produce clinically significant electrolyte shifts." (T. 984, 20-24). Dr. Peura noted that Borody '268 describes taking the solid form with a glass of water, which is different from a solution, as a solution has mixing and when one takes something with a glass of water there is no mixing. (T. 985, 10-21). According to Dr. Peura, Borody '268 "talks about a . . . solid formulation, there's nothing here to teach an aqueous hypertonic solution, or combining sulfate salts to have an effective safe solution" as described in the '149 patent. (T. 985, 22 through T. 986, 7).

'149 Patent Development

Around the turn of the century (2000), the main alternative to GoLytely and NuLytely was Fleet's Phospho-soda, which was a low volume solution. (T. 458, 6-16). Fleet's Phospho-soda was administered in a split-dosing regimen. (T. 460, 4-6; T. 534, 23 through T. 535, 4). As noted above, the benefit of Fleet's Phospho-soda compared to GoLytely and NuLytely was that patient compliance was better due to the low volume of the solution. (T. 458, 17 through T. 459, 5). On the other hand, there was anecdotal information that some patients who used Fleet's Phospho-soda incurred side effects or injuries to the kidney, electrolyte derangements and in some cases death. (T. 233, 23 through T. 534, 8; T. 459, 6-18; T. 461, 11-14; T. 548, 9-23; T. 554, 18 through T. 555, 5; T. 555, 22 through T. 556, 18; T. 785, 11-15; T. 948, 19 through T. 949, 4; T. 1065, 13-16). Evidently, phosphorus caused the deleterious effects.

As Dr. Peura explained, since the phosphate in sodium phosphate is not readily absorbed, it stays in the intestines and keeps the sodium in the compartment of the intestine. (T. 948, 2-8). The phosphate that is absorbed causes problems because phosphate binds with calcium in the

body, causing bone to form (bone is calcium phosphate). As a result, bone forms in the kidneys and produces kidney stones. (T. 948, 9-18). The formation of calcium phosphate in the kidneys was a major problem with Fleet's Phospho-soda. Initially, it appeared that Fleet's Phospho-soda affected only people with abnormal kidney function, but later reports indicated that people with normal kidney function would incur kidney failure because of Fleet's Phospho-soda. (T. 948, 19 through T. 949, 4).

As such, Dr. Cleveland thought another low volume purgative that was safer would be advantageous. In January 2000, Dr. Cleveland conducted a "mental exercise" during which he tried to envision use of only sulfate salts in a low volume solution for colonoscopy preparation. That is, Dr. Cleveland thought about whether it was practical to create a balanced solution using only sulfate salts. (T. 238, 4-25). Despite his brainstorming, there was no evidence that Dr. Cleveland researched the prior art.

On January 21, 2000, Dr. Cleveland jotted down some notes about his idea of using a mixture of sulfate salts in a purgative. (T. 239, 4-20). Dr. Cleveland relied on the large volume isotonic solutions GoLytely and NuLytely as a standard from which to work since he knew that they were safe and did not cause clinically significant electrolyte shifts. (T. 240, 2-15; T. 322, 4-15). Dr. Cleveland imposed certain parameters on his concept. First, he sought to limit the amount of sodium in the solution because he knew that high amounts of sodium posed a risk to elderly people. (T. 241, 11-17; T. 250, 21 through T. 251, 7). In addition, he sought to prevent potassium loss because it may cause renal failure. (T. 293, 12-15).

In Dr. Cleveland's January 21, 2000 notes, he conceived of a three sulfate salt solution that included sulfuric acid as a salt and Vitamin C. (T. 244, 20-24). He also conceived of using three sulfate salts and sulfuric acid to overcome the solubility problems with calcium sulfate. (T.

245, 3-8). At this point, Dr. Cleveland believed his idea "was going to become an invention." (T. 246, 18-21).

Between January 21, 2000 and March 2000, Dr. Cleveland re-worked his solution by replacing calcium sulfate and sulfuric acid with magnesium sulfate as part of a low-volume solution of sulfate salts. (T. 246, 24 through T. 247, 18). At this point, Dr. Cleveland envisioned a solution using magnesium sulfate in combination with potassium sulfate and sodium sulfate. (T. 247, 1-9).

With this combination of the three sulfate salts in mind, Dr. Cleveland contacted Dr. Fordtran to conduct human studies to test his solutions. (T. 247, 1-24). On March 8, 2000, Dr. Cleveland wrote to Dr. Fordtran requesting his help. The letter reads:

> As we discussed recently, Braintree Labs would like you to develop an oral sodium sulfate based preparation for bowel cleansing. This would ultimately be offered in both a capsule and flavored liquid form. If possible, I would like you to compare this to the Fleet Phosphosoda product in terms of electrolyte and biochemical (PTH) changes, etc. It occurs to me that we could reduce the sodium load somewhat by making use of potassium and magnesium sulfate salts as much as possible. Also, the preparation could be designed such that ½ the dose is taken in the evening and ½ in the morning similar to Phosphosoda (which seems to give a superior prep).
>
> Braintree will of course pay for the studies. I would like you to design them for publication (at the appropriate time). Please let me know what you would need to begin. (DTX 024).

After Dr. Fordtran received Dr. Cleveland's March 8, 2000 letter, he prepared an application to conduct a study with the Baylor Research Institute's Institutional Review Board, as he needed the Board's approval for such research in light of health, safety, and risk issues. (T. 110, 2-9). On December 22, 2000, Dr. Fordtran forwarded Dr. Cleveland a rough draft of the protocol for a proposed study as approved. (T. 110, 10-18).

On January 11, 2001, Dr. Cleveland authorized Dr. Fordtran to proceed with the hypertonic sulfate salt study. (T. 111, 20 through T. 112, 2). Dr. Fordtran conducted the hypertonic sulfate salt study during 2001. Dr. Fordtran studied five different solutions (A, B, C, D and E), as well as Fleet's Phospho-soda. (PTX 001, col. 6, table 1; T. 466, 4-6). In conducting this study, Dr. Fordtran used a "scientific method" of "refinement" and "exploration" to develop the test formulas implementing Dr. Cleveland's idea. (T. 261, 5-12). Dr. Fordtran also described this approach as "trial and error." (T. 464, 13-15). Dr. Fordtran conducted an initial experiment with a starting solution, and then used his judgment about how to modify that solution and redesign the experiment in order to achieve a satisfactory result. This process was repeated based on an analysis of the results in order to achieve the goal solution. (T. 360, 8 through T. 361, 7; T. 464, 13-15).

Dr. Fordtran and Dr. Cleveland made a "starting estimation" of where to begin. (T. 464, 15-16). At first, a low dose of sodium sulfate was administered because they didn't know of anybody who had been administered sodium sulfate in the way that was proposed, and secondly to ensure that the amount being given would not harm the subjects. (T. 464, 16-20). At the time of the tests, Dr. Fordtran's team stayed up all night with each subject during the study (from 7:00 p.m. until noon the next day) in order to closely monitor each subject for unforeseen medical conditions that may have occurred. (T. 114, 17 through T. 115, 4).

Solution A contained 100 millimoles of sodium sulfate, 100 millimoles of magnesium sulfate, 5 millimoles of potassium chloride, and 5 millimoles of potassium bicarbonate. (PTX 001, col. 6, table 1). Dr. Fordtran noted that Solution A contained a combined 200 millimoles of sulfate, which is about half the number of millimoles of phosphate in Fleet's Phospho-soda. (T. 466, 14-24). "The main reason and the main point of Solution A . . . was having the 200

millimoles of the sulfate." (T. 467, 6-7). Dr. Fordtran knew that sodium phosphate didn't have any potassium in it, so they added some potassium to the solution "to try to counter the loss of potassium that occurs with the phosphate." (T. 467, 8-11). Since one of the problems with phosphate was that hypokalemia occasionally occurred, they altered a likely loss of potassium with adding potassium chloride and potassium bicarbonate. (T. 467, 11-18).

With regard to Solution B, that solution contained 125 millimoles of sodium sulfate, 125 millimoles of magnesium sulfate, and 12.5 millimoles of potassium sulfate. (PTX 001, col. 6, table 1). Dr. Fordtran noted that an analysis of the results of Solution A revealed that it produced diarrhea as necessary, but not as much as Fleet's Phospho-soda. (T. 468, 6-9). As a result, Dr. Fordtran concluded that the sulfate had to be increased. (T. 468, 10). Since he wanted to keep the salt content as low as possible, he was not opposed to the use of potassium chloride and potassium bicarbonate, but he favored the addition of potassium sulfate, as well as increasing the amount of sodium sulfate and magnesium sulfate. (T. 468, 10-20). As Dr. Fordtran testified, he was slowly raising the amount of sulfate, and eliminating the absorbable salts, and substituting in potassium as potassium sulfate to compensate for the losses of potassium. (T. 468, 20-23).

In Solution C, there was about half as much Phospho-soda as there is in the Fleet's product. And still, given that amount, there was a substantial increase in the serum phosphorous concentration. To Dr. Fordtran, this meant that even half a dose of the Phospho-soda could yield major elevations of serum phosphate, which was risky and unsafe. As Dr. Fordtran noted, "[w]e . . . wouldn't have pursued putting any phosphate in any of the further solutions." (T. 448, 9-18).

In Solution D, the results were almost satisfactory – the stool volume nearly met the benchmark, and electrolyte changes were clinically insignificant. Solution D contained 142.5 millimoles of both sodium sulfate and magnesium sulfate, and 23.75 millimoles of potassium

sulfate. The '149 Patent notes that "[a] further increase in the ingested amounts of salts would likely be effective but, we were concerned about taste problems." (PTX 0001, col. 10, ll. 28-34).

With respect to Solution E, refinements to solution D were made. PEG was added and the potassium sulfate was slightly reduced. (PTX 0001, col. 10, ll. 35-36). Solution E produced an average fecal output that slightly exceeded the Phospho-soda benchmark, and the taste was acceptable. (PTX 0001, col. 10, ll. 37-39).

In August, 2001, Dr. Fordtran drafted a study report summarizing the results of the hypertonic sulfate salt study. (T. 113, 10-18; DTX 29).

On April 30, 2002, Braintree filed U.S. Patent Application No. 10,135,857, and on September 20, 2005, the U.S. Patent and Trademark Office (PTO) issued the '149 Patent.

On July 1, 2008, Braintree filed its New Drug Application (NDA) No. 22-372 for SUPREP with the Food and Drug Administration (FDA).

On October 15, 2008, Braintree requested an ex parte reexamination of the '149 patent; and on June 30, 2009, the PTO issued an Ex Parte Reexamination Certificate, which cancelled claims 1, 6, 8, 9, 13, 14, 17 and 21, and amended claims 2, 3, 4, 7, 10, 15, and 18. The phrase "a small volume" in claims 15 and 18 was amended in the Ex Parte Reexamination Certificate to "from about 100 ml to about 500 ml."

On August 5, 2010, the FDA approved Braintree's NDA No. 22-372 for SUPREP.

OBVIOUSNESS

Burden of Proof and Standard of Review

Novel argues that claims 15, 16, 18, 19, 20 and 23 of the '149 Patent are invalid for obviousness. The ultimate decision concerning nonobviousness is a question of law, but that decision is based on the totality of the evidence, which includes specific factual determinations.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966). A product is "not patentable if it would have been obvious to persons skilled in the art when the invention was made." *Schwartz, Patent Law and Practice* (7th Edition 2011), at p. 93. Generally, a patent may be obvious if it lacks skill and ingenuity that characterizes a patentable invention. However, "a nonobvious invention can arise from systemic experimentation as well as from a flash of creative genius." *Id.* at 95. "Of course, the correct test of invention or nonobviousness focuses on the teachings of the prior art as a whole, not the disclosures of individual references taken singly." *Bayer Schering Pharma AG*, 2008 U.S. Dist. LEXIS 15917 at * 59 (*quoting* 2-5 Chisum on Patents § 5.04, n.14).

The Court evaluates obviousness based on factors set forth in two Supreme Court cases, *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007) and *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The factors are: (1) "the scope and content of the prior art"; (2) the "differences between the prior art and the claims"; (3) "the level of ordinary skill in the pertinent art"; and (4) "[s]uch secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc." *KSR Int'l Co.*, 550 U.S. at 406 (*citing Graham*, 383 U.S. at 17-18).

For a patent to be held invalid due to obviousness, there must be clear and convincing evidence supporting that conclusion. *See PharmaStem Therapeutics Inc. v. ViaCell Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007). The U.S. Supreme Court has defined "clear and convincing evidence" as evidence that satisfies the Court that there is an "abiding conviction that the truth of its factual contentions are highly probable." *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984) (internal quotation marks omitted). This is a higher burden of proof than with other types of civil cases (preponderance of the evidence); and the burden emanates from Congress's deference to prior administrative actions. Novel has the burden to prove obviousness by clear and convincing evidence. The '149 Patent is presumed valid. 35 U.S.C. § 282. "The presumption of

validity is based on the presumption of administrative correctness or actions of the agency charged with examination of patentability." *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.* 98 F. 3d 1563, 1569 (Fed. Cir. 1996). The burden of persuasion remains with Novel and does not shift to Braintree, the patent holder. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F. 2d 1530, 1534 (Fed. Cir. 1983); *Jones v. Hardy*, 727 F. 2d 1524, 1528 (Fed. Cir. 1984).

The Differences Between the Prior Art and the Claims

Having already discussed the level of ordinary skill in the pertinent art and the scope and content of the prior art in earlier sections of this Opinion, the Court turns to the differences between the prior art and the asserted claims of the '149 Patent. As part of this analysis, the Court will initially address the credibility of the witnesses who testified at trial.

In this case, the Court is the sole evaluator of the credibility of the witnesses. Generally, the Court assesses the credibility of witnesses and deduces facts from direct and circumstantial evidence. Like a jury, the Court determines the trustworthiness of testimony by assessing the demeanor of the witnesses and whether their statements were honest and forthright. In assessing the credibility of witnesses, the Court employs the same factors as a jury is instructed to use during its deliberations. *See Bayer Schering Pharma*, 2008 U.S. Dist. LEXIS 15917 at *43-44 (*citing* Third Circuit Model Jury Charges §1.7). These factors are:

> (1) the opportunity and ability of the witness to see or hear or know the things the witness testifies to; (2) the quality of the witness's understanding and memory; (3) the witness's manner while testifying; (4) whether the witness has an interest in the outcome of the case or any motive, bias or prejudice; (5) whether the witness is contradicted by anything the witness said or wrote before trial or by other evidence; (6) how reasonable the witness's testimony is when considered in the light of other evidence that [we] believe; and (7) any other factors that bear on believability.

Air Sea Int'l Forwarding, Inc. v. Global Imports and Trading, Inc., 2008 U.S. Dist. LEXIS 96318, * 15-16 (D.N.J. November 14, 2008) (*citing* Third Circuit Model Jury Charges §1.7).

In this case, there were two knowledgeable experts, and other fact witnesses in the areas of purgatives and gastroenterology, as well as some well qualified business persons. Leading the debate over validity of the '149 Patent were the two expert witnesses, Dr. Johanson and Dr. Peura. Although they both presented cogent arguments, the Court found Dr. Peura to be more credible than Dr. Johanson. Dr. Peura articulated that the prior art did not direct a PHOSITA to combine sodium sulfate, magnesium sulfate, and potassium sulfate in a small volume hypertonic solution that causes purgation, does not produce clinically significant electrolyte shifts, and does not contain phosphate. (T. 977, 24 through T. 977, 9; T. 994, 22 through T. 996, 3; T. 1024, 23 through T. 1025, 19; T. 1042, 20 through T. 1044, 4; T. 1074, 5-24). The Court discounted Dr. Johanson's testimony on credibility grounds because some of his conclusions did not appear to be as reasonable. Here are some examples:

* Dr. Johanson testified that a PHOSITA would "absolutely" review and rely on the Cockerill patent to find that the '149 Patent was obvious. (T. 518, 18 through T. 521, 15; T. 571, 4-17). The Cockerill patent relates to a patent for a composition fed to lactating sows to improve milk production. Although the Cockerill patent teaches about the use of sodium sulfate, potassium sulfate, and magnesium sulfate, a PHOSITA would not review and rely on a composition to improve milk production in lactating sows when developing a colonoscopy preparation solution. The development of a safe and effective colonoscopy preparatory solution cannot be equated with improving the milk production of lactating sows. As such, Dr. Johanson's conclusion that a PHOSITA would "absolutely" review and rely on the Cockerill patent undermines his credibility.

* While Dr. Johanson found the Jones reference (DTX 280), which is a letter to the editor written in 1892 about the medicinal quality of water of Cooper's Well in Mississippi, to be prior art, his conclusion is perplexing. The Jones reference disclosed that the Cooper's Well water contained sodium sulfate, magnesium sulfate, and potassium sulfate. Since the Jones reference is not an objective test or study, it does not meet scientific standards. Rather, the Jones reference is an anecdote from Dr. Jones's personal experience with drinking the water from Cooper's Well. The reference does not indicate the concentrations of the constituents of the water, or the amount a person had to ingest to achieve the "dark green copious evacuations from the bowels." (DTX 280). Moreover, the Jones reference muses between the constituents of the well water to the beauty of the surroundings of Cooper's Well. Accordingly, the substance given to this reference by Dr. Johanson is suspect.

* Dr. Johanson relies on the Cohen and Race references published in the *Lancet* in 1935. Both are one paragraph references with little detail. Dr. Johanson believes that Cohen and Race disclose the purgative effects of magnesium sulfate. It is difficult to deduce how a PHOSITA would substantively learn from the Cohen and Race letters when the letters are so brief and contain little content.

* Dr. Johanson asserted that Dr. Fordtran and Dr. Cleveland utilized the "Fordtran Roadmap" to formulate SUPREP. According to Dr. Johanson, the Fordtran Roadmap is a process that Dr. Fordtran used to develop GoLytely, NuLytely, and SUPREP. The Fordtran Roadmap entails using known information about purgatives and how they would act in the gastrointestinal tract of the human body, and then modifying (tantamount to "tweaking") the starting material based on one's understanding of the normal operation of salts in the colon after they are taken in a solution by oral administration. (T. 542, 4 through T. 547, 15). Essentially,

Dr. Johanson opined that since the sulfate salts were known purgatives, Dr. Cleveland and Dr. Fordtran merely used routine experimentation to modify the dosage amounts of the sulfate salts used in the solutions they tested in the clinical trial disclosed in the '149 Patent. (T. 542, 4 through T. 547, 15).

While the Fordtran Roadmap is a catchy characterization of the methods employed by Dr. Fordtran and Dr. Cleveland with respect to the invention of SUPREP, Dr. Johanson's conclusion falls apart when analyzed against the facts. The state of the art in the 1970's illustrates the point because it takes more than a modification to develop a purgative. (See, *supra* p. 15-16). For instance, sodium chloride was initially used as a purgative; however, after being used for some time, it was discovered that using sodium chloride caused congestive heart failure. Second, non-absorbable sugar (mannitol) was added to salt solutions to hold water, a seemingly reasonable strategy, but the bacteria fermented the sugar producing methane or hydrogen which resulted in explosions occurring inside the patient. Third, PEG was added to the purgative in order to reduce the salt and improve the taste of the solution; however, the PEG caused a glistening effect of the colon as seen through the colonoscope which downgraded the quality. And lastly, Fleet's Phospho-soda caused heart and renal failure, a result that no scientist foresaw from the use of phosphate. Since all of these "would be" improvements had side effects, it appears that the combination and dosage of purgatives requires detailed experimentation to develop. The skill demonstrated by Dr. Fordtran and Dr. Cleveland requires more than a mere modification through routine experimentation as Dr. Johanson opined. The Court gave little weight to the process called the Fordtran Roadmap as a credible characterization of the work of Dr. Fordtran and Dr. Cleveland.

* Dr. Johanson gives weight to the pre-colonoscopy prior art. This is questionable because after the development of the colonoscopy, there was a need for an effective purgative to be administered immediately before the procedure. The identification of elements used prior to the colonoscopy for other diverse purposes does not seem to adequately fill the expectation. Moreover, the testimony of Dr. Fordtran and Dr. Peura was more convincing that Dr. Johanson. Dr. Fordtran's work showed deliberate systematic experimentation of gastroenterological matters where the slightest modification of a salt may cause severe health effects. Moreover, any modification to a purgative solution is a risky venture and it cannot be expected to remain consistent within the human body. Earlier in this opinion, it was noted that Dr. Fordtran testified that his team monitored patients all night long since sodium sulfate had never been administered to patients in such a way. This is far different from the "tweaking" or "modifying" that Dr. Johanson suggests.

Accordingly, after evaluating the prior art as a whole and employing the standard of clear and convincing evidence, the Court finds that the asserted claims of the '149 Patent would not have been obvious to a PHOSITA in April 2002 based on the disclosures of the prior art, and scientific experimentation of Dr. Cleveland and Dr. Fordtran.

ANTICIPATION

Novel contends that Hechter anticipates the disputed claims of the '149 Patent. A patent claim is anticipated only if each and every element in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 (Fed. Cir. 1987); *see also Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). To establish anticipation by inherency, a defendant must establish that the reference necessarily includes the unstated limitation that is disclosed within

the patent. *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002). There is no requirement that the prior art reference recognize that an element is inherent. Instead, the test for inherency requires only that the element is necessarily present in the prior art reference, even though it may not be expressly described. *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010). Anticipation must be proven by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238 (2011).

In reviewing the evidence, Dr. Peura's and Dr. Johanson's opinions on anticipation were miles apart. Most notably, it is the difference between Dr. Johanson's reading of Hechter and that of Dr. Peura. According to Dr. Johanson, Hechter inherently discloses the Step 1 Single Liter Solution. This conclusion seems remote, as Dr. Johanson's reliance on the Step 1 Single Liter Solution does not comport with the term of the Hechter patent. It is evident that Hechter requires a mixture of powder with 1 liter of water, and then adding and mixing 3 more liters of water. As such, Hechter discusses isotonic solutions, not hypertonic solutions, which Dr. Johanson incorrectly deduces.

As stated previously, Dr. Peura's interpretation of Hechter is more credible than Dr. Johanson. As such, the Court finds that Novel did not show proof that met the clear and convincing standard.

DEFINITENESS

In its post-trial submissions, Novel contends that the asserted claims of the '149 Patent are invalid on the ground of indefiniteness. The Court defined the term "purgation" to mean "an evacuation of a copious amount of stool from the bowels after oral administration of the solution." (ECF No. 130, p. 11). Novel asserts that neither Dr. Fordtran, one of the inventors of the '149 Patent, nor Dr. Pelham, the Braintree employee responsible for drafting the '857

application, were able to define the word "copious" as it appears in the Court's construction of the term "purgation." (Novel's Proposed Findings of Fact, ¶¶ 208-211; Novel's Proposed Conclusions of Law, ¶¶ 140-147). Accordingly, Novel argues that the asserted claims of the '149 Patent are invalid as indefinite under the requirements of 35 U.S.C. § 112. *Id.*

That statute states, in part: "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." The Federal Circuit has explained that Section 112(b) contains two separate requirements: "first, [the claim] must set forth what the applicant 'regards as his invention,' and second, it must do so with sufficient particularity and distinctness, i.e., the claim must be sufficiently 'definite.'" *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1349 (Fed. Cir. 2002) (*quoting Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1377 (Fed. Cir. 2000)). The purpose of the definiteness requirement is to "ensure that the claims delineate the scope of the invention using language that adequately notifies the public of the patentee's right to exclude." *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed. Cir. 2005) (internal citation omitted). "The definiteness requirement, however, does not compel absolute clarity. Only claims not amenable to construction or insolubly ambiguous are indefinite." *Id.* (internal quotations and citations omitted). Indefiniteness must be proven by clear and convincing evidence. *Id.* (internal citation omitted).

There is no such clear and convincing evidence here. The Court disagrees with Novel's contentions, and finds that the asserted claims of the '149 Patent are definite under the requirements of 35 U.S.C. § 112, ¶ 2, as the Court's claim construction of the term "purgation" is clear. Dr. Fordtran testified that a copious amount of stool "has to be substantial" (T. 388, 20), and that purgation "does not have a defined volume, but it's a large volume." (T. 389, 11-12).

Dr. Pelham testified at his deposition that he believed that "copious" would be not a "small volume of stool." (T. 641, 3-8). Further, the '149 Patent specifies the quantity of stool evacuated after oral administration of each experimental solution. (PTX 001, col. 10, ll. 9-40 and Table 3).

Accordingly, the Court concludes that Novel has not proven by clear and convincing evidence that the asserted claims of the '149 Patent are indefinite on the ground that the term "copious" could not be defined adequately as it is used in the claim term "purgation."[14]

CONCLUSIONS OF LAW

Based on the foregoing facts and law, Novel has not proven by clear and convincing evidence that the asserted claims of the '149 Patent are invalid as obvious, anticipated, or indefinite. An appropriate Order will follow.

Peter M Sheridan

PETER G. SHERIDAN, U.S.D.J.

Dated: June 4, 2013

[14] In a different context, the definition of "copious" may fall within Justice Stewart's wisdom-"I know it when I see it!" *Jacobellis v. Ohio*, 378 U.S. 184, 197 (1963).